**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:

Marchand et al.

Examiner: A. Small

Serial No.: 10/049,284

Group Art Unit: 1626

Filed: June 17, 2002

Title: METHODS FOR PREPARING PERFLUORINATED [18F]-RADIOLABELLED NITROIMIDAZOLE DERIVATIVES FOR CELLULAR HYPOXIA DETECTION

# BRIEF ON APPEAL

**Mail Stop Appeal Brief-Patents**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

*Real Party in Interest*

The present application is assigned to the Universite Catholique de Louvan, by means of an assignment recorded at reel 013091, frame 0948.

*Related Appeals and Interferences*

There are no known related Appeals or Interferences.

*Status of Claims*

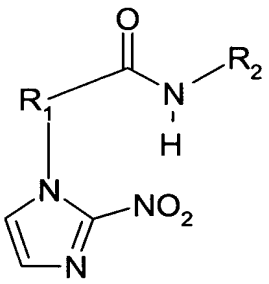
Claims 6-8 and 26-34 are in active prosecution and are on appeal. Claims 1-5, 9, 21 and 35 have been canceled, and claims 10-20 and 22-25 are withdrawn.

*Status of Amendments*

Appellants' Amendment After Final, filed December 23, 2003, has been *entered*, per a telephone conference with the Examiner (it is noted that item 7 of the Advisory Action mailed February 24, 2004, does not indicate such entry).

*Summary of Invention*

The present claims are directed A method for the synthesis of a [$^{18}$F]-labeled perfluorinated-nitroaromatic compound having the formula:




wherein $R_1$ is $CH_2$ and $R_2$ is an alkyl group having up to about 6 halogen atoms, wherein said alkyl group has the formula $CHXCX_2CY_3$ where X is halogen or hydrogen and Y is fluorine, comprising

(1) perfluroinating a first intermediate which is ana amino acid derivative which is N-protected by an imido group or a synthetically equivalent group having a carboxyl function transformed into a dithioester function or a synthetically equivalent persulphurated moiety thereby obtaining a [$^{18}$F]-labeled perfluorinated amino acid derivative which is N-protected by an imido group or a synthetically equivalent group as a second intermediate and

(2) deprotecting the nitrogen function of said second intermediate, resulting in a [$^{18}$F] labeled perfluoroalkyl amine derivative, and coupling 2-(2-nitro-imidazol-1-yl) acetic acid with a [$^{18}$F] labeled perfluoroalkyl amine derivative.

The claims are also directed to diagnostic methods, wherein a $^{18}$F-labeled perfluorinated nitro aromatic compound is produced and used as a diagnostic. See the present specification at page 6, line 26 through page 8, line 6 and page 10, lines 1 through page 11, line 27.

*Issues*

The issues for consideration in this Appeal are the objections to the claims under 37 C.F.R. 1.75(c) and the rejection under 35 U.S.C §102.

*Grouping of Claims*

Separate consideration is respectfully requested for method claims 26-34, separate arguments in support of patentability being given below.

*Argument*

Objection Under 37 C.F.R. 1.75(c)

While it is submitted that there is no express probation on claims depending upon later claims, it is submitted that Appellants' amendment in response to the Final Rejection, discussed above as having been entered, obviates this issue. However, the Advisory Action does not indicate that the objection has been withdrawn. In any event, it is submitted that a careful reading of 37 C.F.R. §1.75(c) does not prohibit such a situation. Subsection (g) of the rule states that the "least restrictive claim should be presented as claim 1, and all dependent claims should be grouped together with the claim or claims to which they refer to the extent practicable." At the outset, it is apparent that this portion of the rule is not mandatory, inasmuch as it states that the claim "should" be presented in such a manner, and not that it "must." Moreover, the section of the rule states that this practice should be performed "to the extent practicable." In the present situation, where a claim numbered 1 has been presented and discarded, of course, the rule cannot be complied with in its entirety. Moreover, it is submitted that it is not practicable to thoroughly rewrite the claims at this point for purposes of economy. It is gently suggested that the technique of amendment of claims, and adjustment of dependencies of earlier dependent claims to depend upon newly added but later independent claims, in fact reduces the burden on the Examiner. If Applicants cancel all existing claims and rewrite them, the examiner would have to first correlate an entirely new schedule of claims with the relevant claims which existed previously, and then compare the claims word for word in order to determine what amendments have been made.

In any event, it is again submitted that this issue is moot.

Rejection Under 35 U.S.C §102

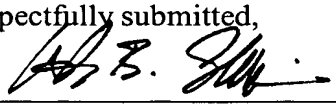
The present claims are directed to a method for obtaining $^{18}$F-labeled halogenated nitroaromatic compounds. Such method involves coupling 2-(2-nitro-imidazole-1-yl) acetic acid with a $^{18}$F-labeled perfluoroalkyl amine derivative. See claim 31. By contrast, to the extent that patentees disclose preparation of perfluorinated nitroaromatic compounds, halogenated 2-nitro-imidazole derivatives are prepared by reacting 2-nitro-imidazole acid derivatives with a halogenated alkyl amine by nucleophilic substitution. The product is a halogenated nitro-imidazole acetamide. Importantly, patentees do not disclose preparation of halogenated nitro aromatic compounds that are $^{18}$F-labeled, in this portion of the patent. Indeed, the only disclosure of such compounds is that at col. 11, lines 30-43, where it is disclosed that "rapid addition of the $F^{18}$ moiety followed by immediate purification and use" is desirable. Thus, as is conventional in the art, patentees simply disclose $^{18}$F-labelling of halogenated nitro-aromatic compounds after those compounds are prepared. This clearly does not anticipate, much less render obvious, a process where compounds are prepared *per se* from $F^{18}$-labeled precursors.

Moreover, it is respectfully submitted that the present method claims are additionally non-obvious over the disclosure of the reference. The cited patent does not disclose or suggest the preparation of compounds in the manner recited, said preparation then being followed by the various biological uses set forth in the method claims. Thus, these claims are also neither anticipated nor suggested by the reference.

In conclusion, it is submitted that ample basis to overturn the rejections of record exists, and the same is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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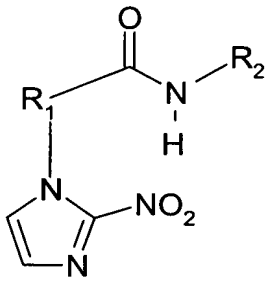
Attorney Docket No.: DCLERC-0001

Date: May 27, 2004

## Appendix

Claim 6 A method for the synthesis of a [$^{18}$F]-labeled perfluorinated-nitroaromatic compound having the formula:



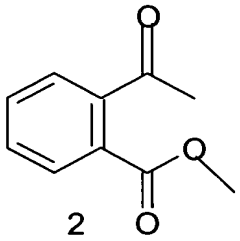

wherein $R_1$ is $CH_2$ and $R_2$ is an alkyl group having up to about 6 halogen atoms, wherein said alkyl group has the formula $CHXCX_2CY_3$ where X is halogen or hydrogen and Y is fluorine, comprising

(1) perfluroinating a first intermediate which is ana amino acid derivative which is N-protected by an imido group or a synthetically equivalent group having a carboxyl function transformed into a dithioester function or a synthetically equivalent persulphurated moiety thereby obtaining a [$^{18}$F]-labeled perfluorinated amino acid derivative which is N-protected by an imido group or a synthetically equivalent group as a second intermediate and

(2) deprotecting the nitrogen function of said second intermediate, resulting in a [$^{18}$F] labeled perfluoroalkyl amine derivative, and coupling 2-(2-nitro-imidazol-1-yl) acetic acid with a [$^{18}$F] labeled perfluoroalkyl amine derivative.

Claim 7 A method for the synthesis of a compound according to claim 6, comprising:

a) adding a THF solution of a compound of formula 2 to a suspension of PYBOP in THF followed by Et3N,



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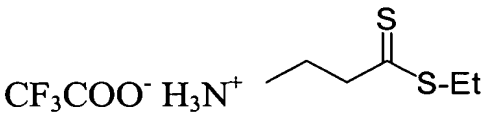
b) adding an amine of formula 1 and $Et_3N$ to the solution obtained in step (a),



c) adding a catalytic amount to the solution obtained in step (b) of pTsOH and refluxing the solution,

d) cooling the solution obtained after step (c) at ambient temperature and adding a sodium bicarbonate solution,

e) extracting the product obtained after step (d) with ethyl acetate and drying and concentrating the product with ethyl acetate,

f) purifying the residue obtained after step (e) by column chromatography on silica gel,

g) removing traces of water by washing the product of step (f) with trifluoroacetic anhydride,

h) reacting ~~said~~ a persulphurated derivative obtained from step (g) with a suitable labeled perfluorinating agent and a suitable oxidant resulting in a compound having a high yield of fluor atom incorporation,

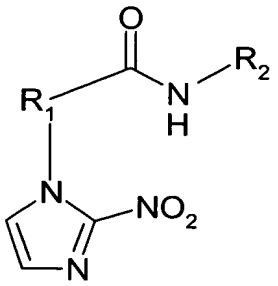
i) deprotecting the nitrogen function, resulting in a perfluoroalkyl amine derivative, and

j) coupling the perfluoroalkyl amine derivative obtained in step (i) with an activated form of 2-(2-nitro-imidazol-1-yl) acetic acid, resulting in the [18F]-labeled ~~or~~ perfluorinated-nitroaromatic compound.

Claim 8 A method according to claim 7 wherein hydrogen fluoride/pyridine complex (HF-Pyridine) is used as a perfluorinating agent and 1,3-dibromo-5,5-dimethylhydantoin (DBH) is used as an oxidant resulting in a compound having a high yield of fluor atom incorporation.

Claim 26 A method for the detection of tissue hypoxia in a patient comprising:

- producing according to the method of claim 6 a [$^{18}$F-labeled perfluorinated-nitroaromatic compound having the formula:



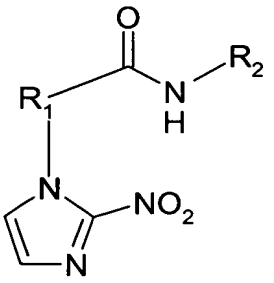

wherein $R_1$ is $CH_2$ and $R_2$ is an alkyl group having up to about 6 halogen atoms, wherein said alkyl group has the formula $CHXCX_2\ CY_3$ where X is halogen or hydrogen and Y is fluorine by coupling 2-(2-nitro-imidazol-1-yl) acetic acid with a [$^{18}$F]-labeled perfluoroalkyl amine derivative according to the method of claim 6;

- quantifying tissue hypoxia in said patient by imagining said patent after having introduced said [$^{18}$F] labeled nitromidazole compound into said patient.

Claim 27 A method according to claim 26 wherein the detection technique used in said method is positron emission tomography.

Claim 28 A method for the detection of tissue hypoxia in a tissue comprising:

- producing according to the method of claim 6 a [$^{18}$F-labeled perfluorinated-nitroaromatic compound having the formula:



wherein $R_1$ is $CH_2$ and $R_2$ is an alkyl group having up to about 6 halogen atoms, wherein said alkyl group has the formula $CHXCX_2\ CY_3$ where X is halogen or hydrogen and Y is fluorine by coupling 2-(2-nitro-imidazol-1-yl) acetic acid with a [$^{18}$F]-labeled perfluoroalkyl amine derivative;

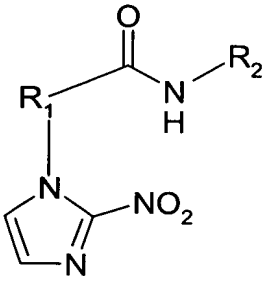
- introducing ~~an~~ said [$^{18}$F] labeled nitroimidazole compound of claim 6 ~~31~~ into a patient,

-removing a tissue sample from said patient, and

-analysing the emission in said tissue sample by autoradiograohy.

Claim 29 A method for the detection of an [$^{18}$F] labeled bioactive compound in a patient comprising:

- producing according to the method of claim 6 a [$^{18}$F-labeled perfluorinated-nitroaromatic compound having the formula:



wherein $R_1$ is $CH_2$ and $R_2$ is an alkyl group having up to about 6 halogen atoms, wherein said alkyl group has the formula $CHXCX_2\ CY_3$ where X is halogen or hydrogen and Y is fluorine by coupling 2-(2-nitro-imidazol-1-yl) acetic acid with a [$^{18}$F]-labeled perfluoroalkyl amine derivative;

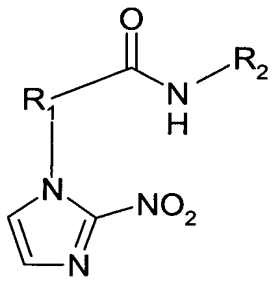
- introducing said [$^{18}$F] labeled bioactive compound according to claim 6 into said patient,

- imaging the presence of said [$^{18}$F] labeled bioactive compound in said patient, and

-optionally, quantifying the presence of said [$^{18}$F] labeled bioactive compound in said patient.

Claim 30 A method for the detection of [$^{18}$F] labeled bioactive compound in a tissue comprising:

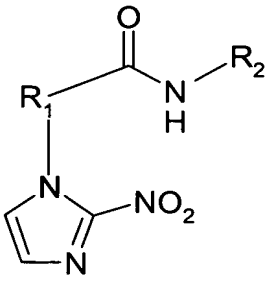
- producing according to the method of claim 6 a [$^{18}$F-labeled perfluorinated-nitroaromatic compound having the formula:



wherein $R_1$ is $CH_2$ and $R_2$ is an alkyl group having up to about 6 halogen atoms, wherein said alkyl group has the formula $CHXCX_2\ CY_3$ where X is halogen or hydrogen and Y is fluorine by coupling 2-(2-nitro-imidazol-1-yl) acetic acid with a [$^{18}$F]-labeled perfluoroalkyl amine derivative;

- introducing an [$^{18}$F] labeled bioactive compound of claim 6 ~~31~~ into a patient,
- taking a tissue sample from said patient, and
- analysing the emission in said tissue sample by autoradiography.

Claim 31 A method according to claim 6, wherein said coupling is a classical peptide coupling using a derivative of 2-(2-nitro-imidazol-1-yl) acetic acid in which the OH group of the carboxyl function has been replaced by a good leaving




Claim 32 A method according to claim 6, wherein the compound has a specific radioactivity of 1 ~~and~~ to 30 Ci/.

Claim 33 A method according to claim 6, wherein the compound has the formula 2-(2-nitro-1H-imidazol-1-yl)-N-(3,3,3-trifluoropropyl) acetamide ([$^{18}$F]-EF3).

Claim 34 A method according to claim 6, wherein the compound has the formula 2(2-nitro-1H-imidazol-1-yl)-N-2,2,3,3,3-pentafluoropropyl) acetamide ([$^{18}$F]-EF5).